COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Efavirenz Xiromed 600 mg film-coated tablets (efavirenz)

NL/H/5216/001/MR

Date: 14 December 2022

This module reflects the scientific discussion for the approval of Efavirenz Xiromed 600 mg film-coated tablets. The procedure was finalised at 3 March 2022. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of medicinal Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Efavirenz Xiromed 600 mg film-coated tablets, from Medical Valley Invest AB.

The product is indicated in antiviral combination treatment of human immunodeficiency virus-1 (HIV-1) infected adults, adolescents and children 3 months of age and older and weighing at least 3.5 kg.

A comprehensive description of the indications and posology is given in the SmPC.

This mutual recognition procedure concerns a generic application claiming essential similarity with the innovator product Sustiva, 600 mg film-coated tablets (Bristol-Myers Squibb Pharma EEIG, UK), which has been registered in the EEA since 18 May 1999 (EU/1/99/110/008-010).

A national marketing authorisation was granted for Efavirenz Xiromed 600 mg film-coated tablets on 05 January 2016 in the Netherlands (RVG 117222).

The concerned member states (CMS) involved in this procedure were Denmark and Sweden.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Efavirenz Xiromed is a yellow, capsule-shaped, biconvex, film-coated tablet, debossed with 'H' on one side and 'E8' on the other side. Each tablet contains as active substance 600 mg efavirenz.

The tablets are packed in white opaque high-density polyethylene (HDPE) bottles with child-resistant polypropylene (PP) caps, white opaque PVC/aluminium or aluminium/aluminium blisters, or perforated unit dose blisters made from PVC/aluminium or aluminium/aluminium.

The excipients are:
Tablet core – microcrystalline cellulose, lactose monohydrate, sodium lauryl sulphate (E487), croscarmellose sodium (E468), hydroxypropyl cellulose (E463) and magnesium stearate (E572);
Film coating – hypromellose (E464), titanium dioxide (E171), yellow iron oxide (E172) and macrogol (E1521).

II.2 Drug Substance

The active substance is efavirenz, an established active substance described in the United States Pharmacopoeia (USP). Efavirenz is a white to slightly pink crystalline powder, with ten polymorphic forms. The material used in the current drug product concerns Form-I, this form is soluble in methanol and practically insoluble in water. Efavirenz is not hygroscopic (able to absorb or adsorb water).

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process

Efavirenz (Form-I) is manufactured by one ASMF-holder using three different synthetic routes. Efavirenz is synthesized in three or five steps, depending on the followed route. Analyses on potential and possible impurities have been adequately performed according to ICH Q3D and discussed. Efavirenz has been adequately characterized. Acceptable specifications for the solvents and reagents used in the manufacturing process have been adopted. The manufacturing processes have been adequately described.

Quality control of drug substance

The drug substance specification has been established in-house by the MAH, based on the specifications of the drug substance manufacturers, with additional requirements for microbiological purity and particle size. In-house methods and limits are described for the non-compendial excipients' tests. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for one pilot and two production scaled batches of efavirenz.

Stability of drug substance

Stability studies of the ASMF at long-term and accelerated conditions did not show any up- or downward trends indicating that the batches remain stable throughout the tested period. The re-test periods varying from 24 to 60 months are acceptable, based on available long-term stability studies. No specific temperature restrictions are required as the drug substance is found stable when stored at stated conditions.

II.3 Medicinal Product

Pharmaceutical development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients is

justified and their functions explained. The test product was compared to the innovator product with respect to active substance and dissolution. A suitable dissolution method was developed for routine dissolution testing. The influence of excipient concentrations on the dissolution profiles of the uncoated tablet cores was studied. Dissolution of the developed formulation was repeated with film-coating, compared with the reference product. The comparative dissolution data between the two batches used in the bioequivalence study show that for both the test and the reference product more than 85% is dissolved after 30 minutes. The pharmaceutical development of the product has been described in sufficient detail.

Manufacturing process

The manufacturing process is considered a standard process and it has been validated according to relevant European guidelines. The process includes sifting, dry mixing, wet granulation, (air) drying, sifting and milling, extra granular sifting, (pre)-lubrication, blend sample analysis, compression, film-coating, finished product analysis, and packaging. Process validation data on the product have been presented for two full scale batches in accordance with the relevant European guidelines.

Control of excipients

The tablet core excipients comply with the Ph. Eur. and the excipients of the tablet coating complies with an in-house specification. The coating system is a commercially available mixture of excipients which are all described in the Ph. Eur. All specifications are acceptable.

Quality control of drug product

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for description, identity, average weight, water content, dissolution, uniformity of dosage units, related compounds, assay, microbiological examination and identification of colourant. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. The release specification is identical to the shelf life specification, except for water content. Water content was tested in accordance with the Ph. Eur. The drug product specification is acceptable.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from two full scale batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided on two full scaled batches stored at 25°C/60% RH (18 months) and at 40°C/75% RH (6 months), stored in Alu/Alu-blister packs, PVC/Alu-blister packs and in HDPE-containers with a PP cap. Two full scaled batches were stored at 25°C/60% RH (12 months) packed in HDPE-bags in triple laminated bags (bulk). The conditions used in the stability studies are according to the ICH stability guideline.

The stability results showed no up- or downward trends of all batches after storage for up to 18 months under long term and up to 6 months under accelerated conditions. Based on the accelerated and real time stability data, a shelf-life of 30 months is justified, without the need for special storage conditions. No additional stability data are needed to fully support the shelf-life and storage conditions. In-use stability for 30 days for the HDPE-containers has been sufficiently demonstrated.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Certificates of suitability issued by the EDQM have been provided for lactose monohydrate, and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Efavirenz Xiromed has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Efavirenz Xiromed is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Sustiva, which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Efavirenz is a well-known active substance with an established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies were required, besides the bioequivalence study discussed below.

IV.2 Pharmacokinetics

The MAH conducted one bioequivalence study in which the pharmacokinetic profile of the test product Efavirenz Xiromed 600 mg film-coated tablets (Medical Valley Invest AB, Sweden) is compared with the pharmacokinetic profile of the innovator product Sustiva, 600 mg film-coated tablets (Bristol-Myers Squibb Pharma EEIG, UK).

The choice of the reference product in the bioequivalence study has been justified. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Bioequivalence study

Design

A single-dose, open label, balanced, randomized, two-treatment, two-period, two-sequence, cross-over bioequivalence study was carried out under fasted conditions in 42 healthy male subjects, aged 19 – 38 years. Each subject received a single dose (600 mg) of one of the two efavirenz formulations. The tablet was orally administered with 240 mL water after an overnight fast of at least 11 hours. There were two dosing periods, separated by a washout period of 28 days.

Blood samples were collected pre-dose and at 1, 2, 2.33, 2.66, 3, 3.33, 3.66, 4, 4.33, 4.66, 5, 5.5, 6, 7, 8, 10, 12, 16, 24, 36, 48 and 72 hours after administration of the products.

Fasting conditions are in accordance with the SmPC, which states that Efavirenz Xiromed should be taken on an empty stomach. The design of the study is acceptable.

Analytical/statistical methods

The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results

Nine subjects dropped out or were withdrawn from the study. One subject did not complete Period I of the study due to vomiting. At the start of Period II, four subject did not report to the facility, two subjects were withdrawn due to non-compliance, and one subject withdrew

from the study on their own accord. One more subject withdrew voluntarily post-dose during Period II. This left a total of 33 subjects eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD) of efavirenz under fasted conditions.

Treatment N=33	**AUC_{0-72h}** (mg.h/mL)	**$AUC_{0-\infty}$** (mg.h/mL)	**C_{max}** (mg/mL)	**t_{max}** (h)
Test	54.81 (± 17.65)	--	3.27 (± 1.11)	3.2 (± 1.05)
Reference	57.91 (± 17.51)	--	3.16 (± 1.34)	3.0 (± 1.15)
***Ratio (90% CI)**	0.94 (0.87 – 1.01)	--	1.05 (0.96 – 1.16)	--

AUC_{0-72h}	Area under the plasma concentration curve from administration to 72 hours. AUC_{0-72h} can be reported instead of AUC_{0-t}, in studies with sampling period of 72 hours, and where the concentration at 72 hours is quantifiable. Only for immediate release products.
$AUC_{0-\infty}$	Area under the plasma concentration curve extrapolated to infinite time. $AUC_{0-\infty}$ does not need to be reported when AUC_{0-72h} is reported instead of AUC_{0-t}
C_{max}	maximum plasma concentration
t_{max}	time for maximum concentration
*	ln-transformed values

Conclusion on bioequivalence study

The 90% confidence intervals calculated for AUC_{0-72h} and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study, Efavirenz Xiromed is considered bioequivalent with Sustiva.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

IV.3 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Efavirenz Xiromed.

Table 2. Summary of safety concerns as approved in RMP

Important identified risks	• Psychiatric and nervous system symptoms • Skin rash and severe skin reactions • High-grade hepatic enzyme elevation and severe hepatic events • Fetal neural tube abnormalities (including m meningomyelocele, spina bifida, or hydrocephalus) associated with first trimester exposure to EFV • Alteration in blood levels and CYP2B6 generic polymorphism
Important potential risks	• Urolithiasis/Nephrolithiasis • Malignant neoplasms
Missing information	• Use in paediatric populations (< 3 years old) • Use in in elderly patients • Patients with renal impairment • Patients with hepatic impairment

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Sustiva. No new clinical studies were conducted besides the bioequivalence study. The MAH demonstrated through this bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to the innovator product, Sustiva (EU/1/99/110/008-010). The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet and no readability test was needed.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Efavirenz Xiromed 600 mg film-coated tablets has a proven chemical-pharmaceutical quality and is a generic form of Sustiva, 600 mg film-coated tablets. Sustiva is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Efavirenz Xiromed with the reference product, and have therefore granted a marketing authorisation. The mutual recognition procedure was finalised with a positive outcome on 3 March 2022.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
N/A	N/A	N/A	N/A	N/A	N/A